Remarks

Claims 1, 4-23, 25-32, 67, 70, 92, 93, and 95-105 were examined in this case. All claims were rejected in the Office Action. The present Response amends claims 1, 8-12, 14, 32, and 98-100, cancels claims 4-7, 10-11, 75-91, 96, and 101-102, and adds claims 106 and 107. Each of the objections and rejections levied in the Office Action is addressed individually below.

Support for the Amendments

Support for new claims 106 and 107 can be found in the specification at page 32, lines 20-22. Support for the amendment to claims 8 and 9 can be found in the specification at page 26, line 19 to page 27, line 10 and Figures 22 and 23, which states,

> Competition analysis (Figure 22) has been employed to define antibodies with similar binding sites in HCV E2. Seven HMAbs were biotinylated and the binding of the biotinylated antibodies to HCV E2 in the presence of increasing amounts of competing HCV HMAbs was determined. Antibodies that cross-competed significantly were grouped together. Regions of HCV E2 that contained the binding sites were localized using a series of HCV E2 deletion constructs (Figure 23). Four competition groups were defined. Group I consisted of five HMAbs, CBH-2, -8E, -5, -8C, and -11. Antibodies from this group inhibit binding of HCV E2 to CD81 and recognize conserved epitopes localized to HCV E2 amino acids 411 to 644. Group II consists of HMAbs CBH-7 and XTL-U68, which recognize a highly conserved epitope located between HCV E2 amino acids 470-644. Antibodies from groups I and II exhibited minimal cross-competition. Group III consisted of three antibodies, CBH-4G, -4B, and -4D, that do not inhibit binding of HCV E2 to CD81 and recognize epitopes between HCV E2 amino acids 470 to 644.

New Objection

The Examiner states that the Amendment filed February 10, 2003 is objected to under 35 U.S.C 132 because it introduces new matter into the disclosure. The added material which the

Examiner asserts is not supported by the original disclosure is as follows: "The dissociation constants for these antibodies for their epitopes rages from less than 10^{-7} to less than 10^{-8} to less than 10^{-9}M" (page 6, line 14). In response, the material added at page 6, line 14, in the second sentence has been amended to change the K_D ranges to K_D values as recited in original claims 4-7. Support for this amendment can be found in claims 4-7 in the application as filed. Withdrawal of this objection is requested.

Rejections Under 35 U.S.C § 112, Second Paragraph

Claims 32, 67, 70, and 98-100 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Each aspect of this rejection is addressed below.

The Examiner states that claim 32 is indefinite in reciting "the step of administering the antibody comprises administering more than one different antibody." The Examiner states that it is not clear whether the additional antibody or antibodies must also be an antibody within the scope of claim 1, or whether it or they can be any different antibody. In response, claim 32 has been amended to recite, "The method of claim 30 or 31 wherein in the step of administering, more than one antibody is administered, wherein the antibodies are directed to a conformational epitope of a protein of Hepatitis C virus.." In light of the amendment to claim 32 and our remarks, withdrawal of this aspect of the rejection is requested.

The Examiner states that claims 67 and 70 are indefinite since each claim depends directly or ultimately from canceled claim 66. Claims 67 and 70 have been canceled. Withdrawal of this aspect of the invention is requested.

The Examiner states that claims 98, 99, and 100 are indefinite since each claim depends from canceled claim 94. Claims 98, 99 and 100 have been amended to delete the dependency

from claim 94. Claims 98, 99, and 100 now only depend from pending claims. In light of the present amendment, withdrawal of this aspect of the rejection is requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 4-7 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that while an original claim may be taken to provide written description, the specification does not appear to teach or describe the production and/or selection of antibodies to conformational epitopes of Hepatitis C virus with particular values for binding constants, or characterized according to their binding constants for their epitopes. The Examiner further states that the ranges of values added to the specification constitute new matter and that it is not apparent where antibodies with K_Ds with these values were provided for in the specification as filed. Applicant disagrees.

Applicant has amended the specification to recite the particular values for binding constants as provided in the original claims. No new matter is added by this amendment. Applicant further asserts that one skilled in the art would know how to *produce* and *select* for such antibodies to conformational epitopes of Hepatitis C virus given the teaching of the specification, the original claims, and the knowledge in the art. For example, Example 2 describes antibody screening of potential B cell donors. Example 3 describes the production of antigen-specific human monoclonal antibodies. ELISA assays for measuring antibody binding are described in Example 4. Once such antibodies are identified, any person skilled in the art would know how to measure their binding affinities, as these methods are standard in the art.

Having produced and selected such antibodies, as Applicant has done, one of ordinary skill in the art could easily determine their binding constants. Moreover, it would be reasonable to propose that the binding constants would be less than 10^{-7}M, less than 10^{-8}M, less than 10^{-9}M, or less than 10^{-10} M, as suggested in the as filed claims.

In summary, has Applicant produced and selected for antibodies and provided binding constants that the antibodies were likely to have. It is reasonable that one skilled in the art, with his or her knowledge and experience, could measure with reasonable accuracy the binding affinity of an antibody to an antigen. Having been provided with the antibodies by the teachings of the present specification, taking the steps to measure the binding constants of these antibodies could be done by any person skilled in the art. In light of these facts, withdrawal of this rejection is requested.

Claims 29, 30-32, 67, 70, and 98-100 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention essentially for reasons of record in rejecting claims 29, 30-32, 66, 67, 70, and 98-100 in the previous Office Action. The Examiner asserts that the references cited by the Applicant in Applicants last Response (mailed February 10, 2003) tend to show that the state of the art, at the time the invention was made, supports that lack of predictability in using in vitro neutralization of binding assays to correlate with likelihood of success in treating using anti-HCV E2 antibodies in general, and do not provide any evidence with respect to the use of monoclonal antibodies as claimed in treatment. Applicant disagrees.

Claim 29 recites a pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable excipient. Claim 30 recites a method of treating or preventing HCV infection in a patient, the method comprising steps of: providing a patient infected with HCV or susceptible to HCV infection; and administering to the patient the antibody of claim 1. Claim 31 recites a method of treating a patient exposed to HCV, the method comprising steps of: providing a patient exposed to HCV; and administering to the patient the antibody of claim 1. Claim 98 recites a pharmaceutical composition comprising the combination of claim 92, 93, 95, or 97 and a pharmaceutically acceptable excipient. Claim 99 recites a method of treating or preventing HCV infection in a patient, the method comprising steps of: providing a patient infected with HCV or susceptible to HCV infection; and administering to the patient the combination of claim 92, 93, 95, or 97. Claim 100 recites a method of treating a patient that has been exposed to HCV, the method comprising steps of: providing a patient that has been exposed to HCV; and administering to the patient the antibody of claim 92, 93, 95, or 97.

In the Office Action mailed September 10, 2002 (Paper No. 13), the Examiner asserts that the specification at page 91 shows that some HCV-infected patient sera have antibodies that compete for binding to the eptitopes bound by monoclonal antibodies CBH-2 and CBH-7 and that patients with relatively lower titers of those antibodies belonged to a group with higher median viral load. Specifically, the Examiner point to the statement, "Thus most HCV infected individuals are characterized by low levels of serum antibodies with putative neutralization activity, " and "Therapeutic use of HCV-neutralizing human monoclonal antibodies, *such as* CBH-2 and CBH-7, have the potential to be of value in these individuals" [Emphasis added]. The Examiner then implies that the claims should be limited to CBH-2 and CBH-7.

It is clear from the language in the specification, i.e., "*such as* CBH-2 and CBH-7," that the Applicant intended for antibodies in addition to CBH-2 and CBH-7 to qualify as therapeutic antibodies. Such additional antibodies could easily be identified by simply testing them as CBH-2 and CBH-7 were tested. Doing so would be a matter of mere routine experimentation to one of ordinary skill in the art, having been provided with the anti-HCV E2 antibodies disclosed in the specification and the assays in Example 10. Any person of skill in the art, based on the Applicant's teachings, could perform such an experiment.

Claims 1 and 92, from which the rejected claims depend, have been amended to recite specific antibodies, including CBH-2 and CBH-7. Antibodies CBH-4G, CBH-5, CBH-8C, and CBH-11 could simply be used in the assays described in Example 10 to obtain the results that have been obtained for CBH-2 and CBH-7. Being provided with the teachings of the invention would enable any person skilled in the art to identify these antibodies as antibodies having therapeutic potential. Limiting the claims to only CBH-2 and CBH-7 would unduly limit what the Applicant is entitled based on the discovery.

In light of the above, withdrawal of this rejection is requested.

Non-Statutory Double Patenting Rejection

Claims 1, 4-23, 25-29, 92-98, and 101-105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 and 59 co-pending Application No. 09/430,489 (Our Ref. No. 2002850-0003).

Applicant respectfully refrains from responding to this provisional rejection until such time as it matures into an actual rejection.

Rejections Under 35, U.S.C. § 102(b)

Claims 1, 4, 5, 14, 15, 22, 23, 25, 26, 28, 29, 92, 98, and 101 stand rejected under 35, U.S.C. § 102(b) as being anticipated by Persson et al. (WO 97/40167). Applicant disagrees.

Claim 1 recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype, wherein the antibody is selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitopes as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11. Claim 92 recites a combination of two or more antibodies directed to two or more different conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype, wherein the antibodies are selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitopes as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11. The remaining claims are dependent on claim 1 or claim 92.

Applicant submits herewith a Declaration under 1.132 and Exhibits A-D demonstrating that the antibodies recited the claims are structurally distinct from the antibodies of Persson et al. and have different antigen binding specificities.

Exhibit A provides some general information about how the antigen binding specificity of antibodies is determined. As explained in the Declaration, the antigen binding portion of an antibody, or the Fab fragment, is made up of a heavy chain and a light chain, each having a variable (V) domain and one or more constant (C) domains. As shown in the top portion of the first page of **Exhibit** A, the light chain contains one variable domain (V_L) and one constant domain (C_L) (see page 1 of **Exhibit A**). The heavy chain contains one variable domain (V_H) and

three constant domains (C_H). Each variable domain has three regions that show a high level of amino acid sequence diversity. These "hypervariable regions" (HVRs) are called Complementarity Determining Regions (CDRs) (see page 2, Exhibit A).

Exhibit B is a paper by Xu and Davis, which shows that the diversity in antigen-binding specificity of an antibody is determined mostly by the diversity in sequence of CDR3 of the V_H chain alone. As stated in the Declaration, Xu and Davis created mice constrained to use a single V_H gene (V_H 5-51), but full CDR3 diversity to generate their B cell repertoire. Mice were challenged with a variety of protein and hapten antigens and the development of primary and memory immune responses monitored. (See Exhibits "Experimental System," page 37-38 and "Experimental Procedures," page 43.) As stated in Declaration, Figure 2 shows that these mice respond to antigen challenge with a "normal" immune response (see also page 39, column 1). Xu and Davis also showed that monoclonal antibodies could be generated against a variety of antigens in these mice. When they sequenced the genes encoding the variety of monoclonal antibodies, they found that their sequences differed predominantly in the CDR3 region. Xu and Davis conclude that "the highly diverse CDR3 loops are the key determinant of specificity to antigen recognition."

Persson et al. disclose four Fab molecule clones, 1:5, 1:7, 1:11, and L3. The deduced amino acid sequence of the V_H chain of each antibody is shown in Figures 1A-1D (SEQ ID NOs: 1-4). The deduced amino acid sequence of the V_L chain of each antibody is shown in Figures 2A-2D (SEQ ID NOs: 5-8). The CDR regions (CDR1, CDR2, CDR3) are indicated.

The genes encoding the V_H chain of the antibodies of the present invention were also sequenced, as described in the Declaration and in **Exhibit C**. Specifically, the amino acid sequences of the V_H and V_L genes of CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C,

CBH-8E, CBH-11, CBH-2, and CBH-17 were determined. **Exhibit D** shows alignments of the deduced amino acid sequences of the antibodies of Persson et al. (SEQ ID NOs: 1-4 and 5-8) and the deduced amino acid sequences of the antibodies of the present invention (CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17) (see pages 1-4 and 9-12 of **Exhibit** D). As explained in the Declaration, the alignments show that the sequences of the Persson et al. antibodies are different from the sequences of the antibodies of the invention. Furthermore, there are no identical sequences between any of the CDR regions (CDR1, CDR2, or CDR3) of Persson et al. and any of the antibodies CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, or CBH-17.

Dr. Foung, an expert in the field, reasoned that because the sequence of CDR3 primarily determines the antigen binding specificity of antibodies (Xu and Davis, **Exhibit B**) and because each of the CDR1, CDR2, and CDR3 sequences of our antibodies are different from the CDR1, CDR2, and CDR3 sequences disclosed in the Persson et al. reference, the antigen binding specificities of our antibodies are distinct from the antigen binding specificities of Persson et al. Thus, the antibodies are structurally distinct from one another and have different binding specificities.

Anticipation under 35 U.S.C. 102 requires that the invention disclosed by the prior art reference must be identical to the claimed invention in each and every aspect. As stated in *Hybritech Inc. v. Monoclonal Antibodies, Inc,* 802 F.2d 1367,231 U.S.P.Q. 81 (Fed. Cir. 1986), "[I]t is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." Nowhere do Persson et al. disclose a monoclonal antibody the same as presently claimed. Therefore, the Persson et al. publication cannot anticipate the claimed invention and withdrawal of this rejection under 35 U.S.C. § 102(b) is requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 8-13 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Persson et al. The Examiner states that the antibodies of Persson et al. reasonably appear to be the same or only slightly different from the antibodies of claim 8-13. The Examiner states that the arguments made in the last Response were not found persuasive because they rely on limitations not found in the claims, i.e., the rejected claims do not require hybridomas. The Examiner further states that Persson's antibodies came from an HCV infected donor, and they behave the same way in neutralization assays as Applicants antibodies. The Examiner concludes that the Applicant has provided neither persuasive argument nor factual evidence that Applicant's antibodies as claimed are structurally or functionally different from Persson's.

Claim 8 recites an antibody that binds to a conformational epitope within amino acids 411 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody binds to the E2 protein of Hepatitis C virus of more than one genotype, wherein the antibody is selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitopes as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11. Claim 9 recites an antibody that binds to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype, wherein the antibody is CBH-4G, or binds to the same conformational epitopes as CBH-4G. Claim 12 recites an antibody that binds to the epitope recognized by CBH-

2, -4D, -4B, -4G, -5, -7, -8C or -11. Claim 13 recites an antibody wherein the antibody competes with CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -11 for binding to its epitope.

Applicant submits herewith a Declaration under 1.132 and Exhibits A-D demonstrating that the antibodies recited in claims 1 and 2 are structurally distinct from the antibodies of Persson et al. and have different antigen binding specificities than the antibodies disclosed in the Persson et al. reference. As described above, Persson et al. discloses four antibodies whose heavy and light chain sequences appear in Figures 1A-1D and 2A-2D (SEQ ID NOs: 1-8). The sequences of the Persson et al. antibodies differ substantially from the sequences of the antibodies of the present invention, which are illustrated in Figure 1 of **Exhibit C**. Sequence alignments of the variable regions of the heavy (V_H) and light (V_L) chains of the Persson et al. antibodies and the antibodies of the invention (CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17) are provided in **Exhibit D**.

Comparing the amino acid sequences of Persson et al. to the amino acid sequences of CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17, it is clear that none of the sequences are the same. Furthermore, there is a lack of consensus sequences in the CDR regions, drawing particular attention to CDR3. This is proof that the antibodies of the present claims are not the same as the antibodies disclosed by Persson et al.

The Declaration provided by Dr. Foung and submitted herewith shows that the antibodies of the present invention are not only entirely different in amino acid sequence, but also have different binding specificities as deduced by the differences in the CDR binding regions. As described in the Declaration, **Exhibit B** provides evidence that antibody-binding specificity is determined primarily by the diversity of CDR3 of V_H "alone" (page 40 column 1). **Exhibit B** shows that mice constrained to use a single V_H gene, but full CDR3 diversity, generated a

"normal" immune response to different protein and hapten antigens. **Exhibit B** further demonstrates that the mice generated monoclonal antibodies to a variety of antigens. From this data, it was concluded that "the highly diverse CDR3 loops are the key determinant of specificity to antigen recognition" in antibodies. Figure 3 of **Exhibit B** shows a sequence analysis of monoclonal antibodies to different antigens. It is clear that the diversity in sequence of the CDR3 corresponds to the diversity in antigen binding specificity.

Since the Persson et al. antibodies differ so substantially in the amino acid sequence of CDR3, as well as CDR1 and CDR2, from the antibodies of the claims, and because diversity in the CDR3 sequence determines diversity in antigen binding specificity, it can be concluded, as described in Dr. Foung's Declaration, that the antibodies of Persson et al. and the claims differ in antigen binding specificity. As stated in Xu and Davis reference of **Exhibit B**, "diversity at one of these regions, CDR3 of the V_H domain, is sufficient to permit otherwise identical antibody molecules to distinguish between a variety of hapten and protein antigens" (Abstract). Thus, the diversity in the sequences of theCDR1, CDR2, and CDR3 regions of the antibodies of Persson et al. and the present claims is evidence of the diversity in the binding specificity.

In light of the above, withdrawal of this rejection is requested.

Conclusion

Applicant respectfully requests entrance of the present Amendment and consideration of the above Remarks. Applicant submits that the present Response is submitted within two months of the receipt of a Final Office Action in this case. Please charge any fees that may be required, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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